Azithromycin pharmacokinetics and implications for extended doses for treating *Chlamydia trachomatis*

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Background: There is increasing concern about the efficacy of azithromycin for the treatment of genital chlamydia and particularly for anorectal chlamydia. Extended doses has been considered as one option to improve efficacy but the optimal regimen is unclear. A review was undertaken to examine the dose-related pharmacokinetics of azithromycin in anogenital, urogenital and other tissues to provide possible considerations for extended dose regimens that would improve azithromycin's efficacy.

Methods and analysis

- A review of studies reporting the pharmacokinetics of oral azithromycin for urogenital and anorectal tissue were the primary focus but other tissues susceptible to chlamydia infection (excluding eyes) were included.
- Dose administered and key pharmacokinetic parameters were extracted for each study i.e. maximum concentrations (Cmax), time to Cmax (Tmax), area under the concentration-time curve (AUC) for time 0-24 hours (AUC_{0-24}), 0-last time (AUC_{0-last}) and/or 0-infinity ($AUC_{0-\infty}$).
- Dose dependent associations with total drug absorption (Fig 1) and tissue concentrations (Fig 2-4) was presented.
- The pharmacokinetic data was then used to make some suggestions for what might be an appropriate dosing regimen for extended courses of azithromycin.

Results

- Blood/tissue concentrations follow a near-linear, dose-dependent relationship (Fig 1,3,4) and appear non-saturable with short courses.
- Concentrations above MIC were sustained for >7 days in most tissues except for muscle and lymphatic tissue (Fig 2-4). The latter is of concern for treating extracellular replicating chlamydia and LGV.
- High concentrations in saliva (Fig 2) have implications for drug exposure at ano(uro)genital sites via oral sex and rimming.
- Data in gastric mucus (not shown) suggest potential concentrations in rectal mucus which has negative implications for douching.
- pH in rectal tissue may have an effect on azithromycin efficacy (Fig 4)
- Total absorption are dependent more on <u>total dose</u> than duration (Fig 1)
- Short courses (3 days) appears to optimize dosing with a high first dose (e.g. 1g) exploiting drug delivery by phagocytic cells during the acute phase of infection i.e. "hit hard, hit early" (data not shown).

Figure 1: Azithromycin total absorption (blood) by dose ($AUC_{0-\infty}$)

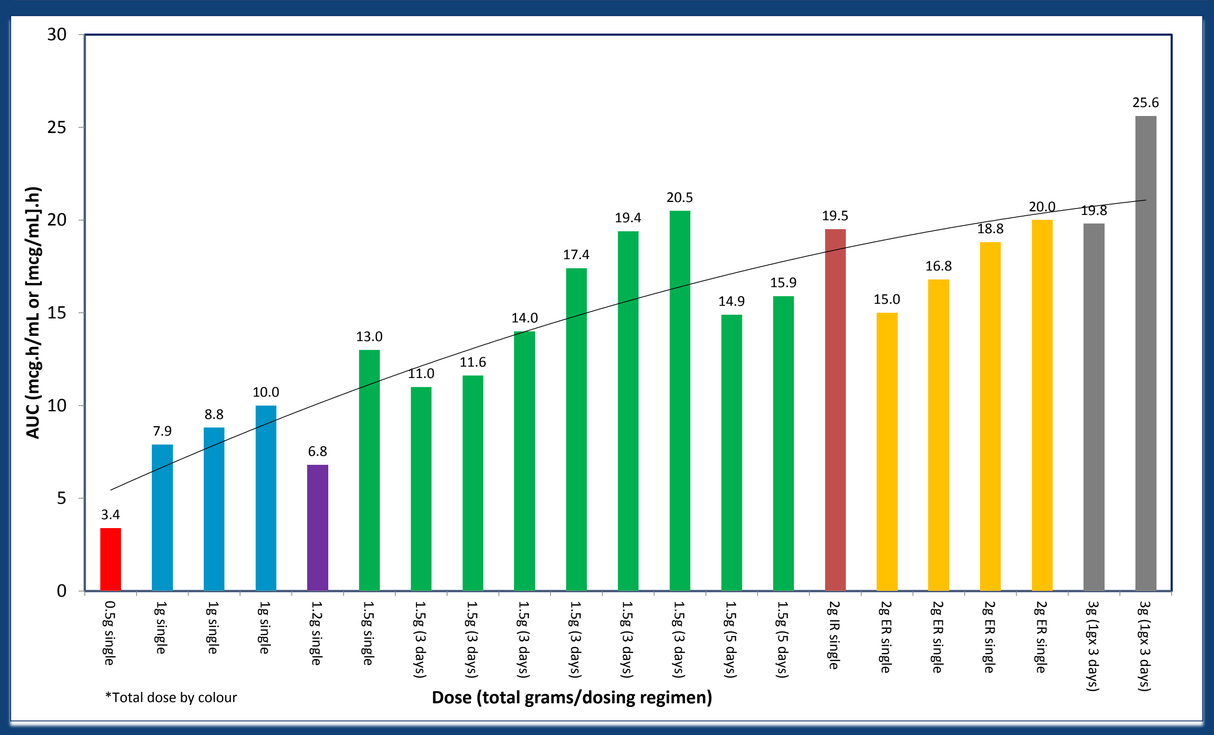

Figure 3: Gynaecological tissue concentrations by dose

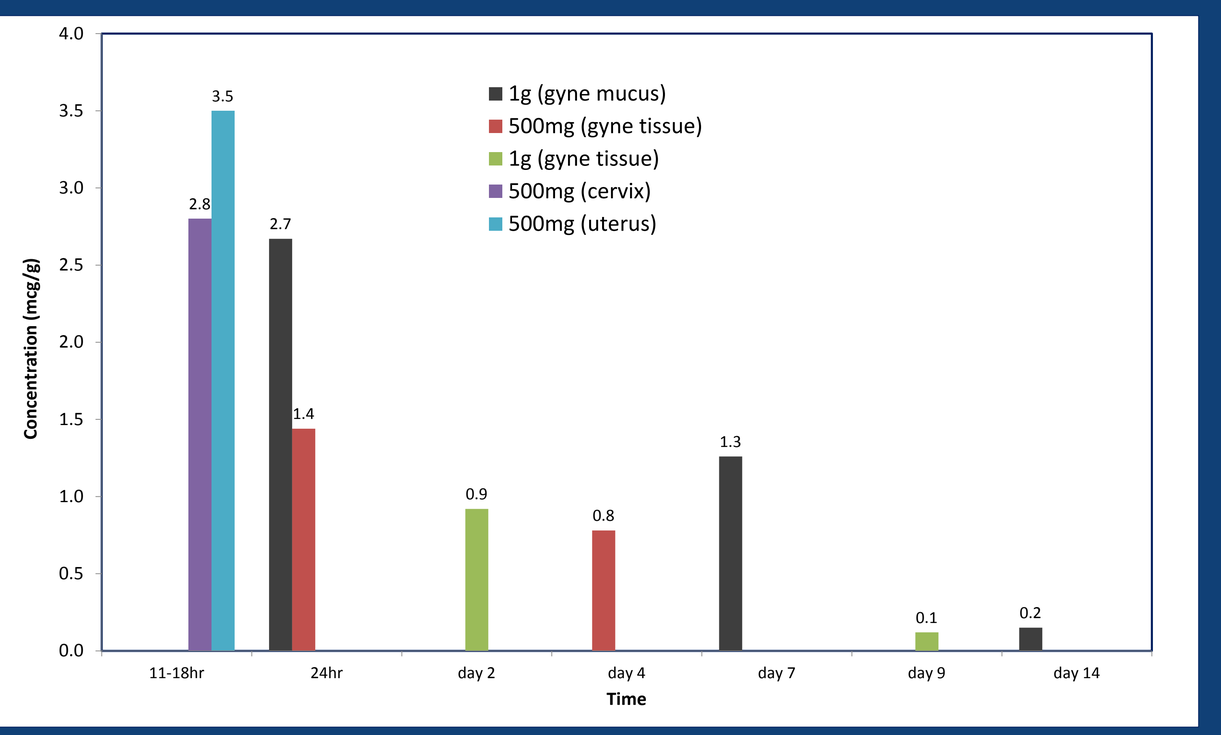

Figure 2: Azithromycin tissue concentrations, by type, following 500mg dose

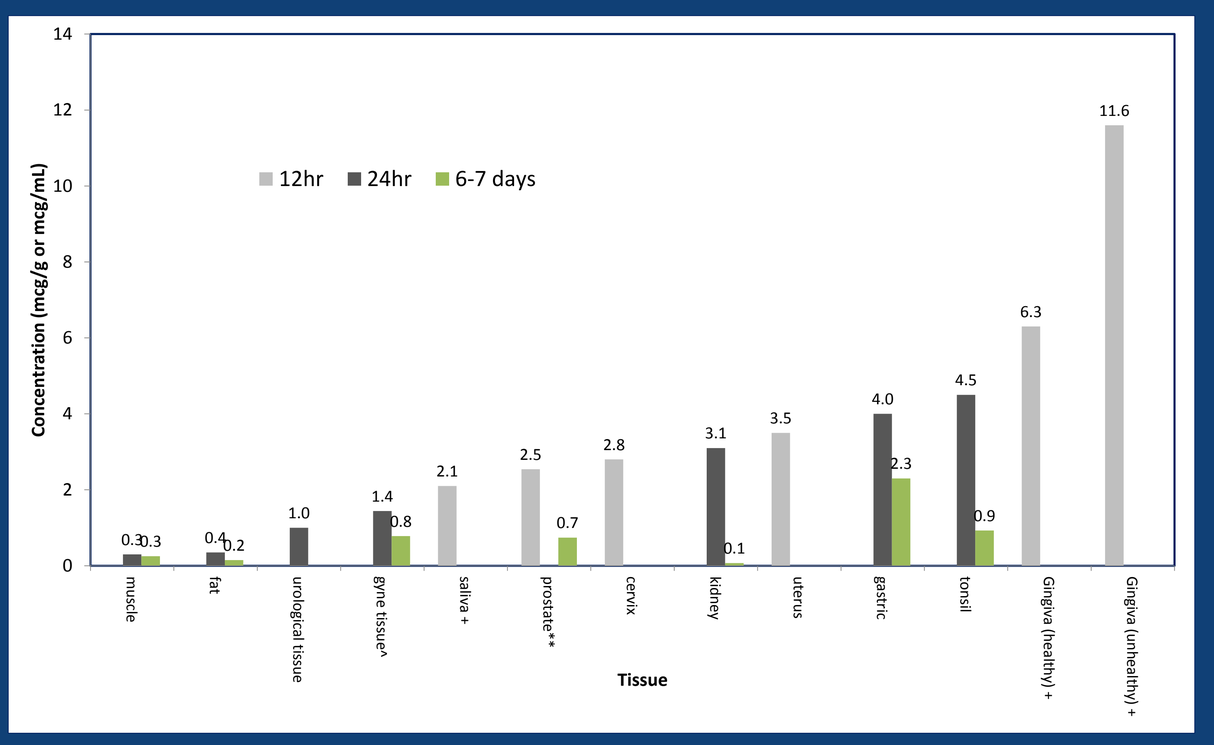

Figure 4: Gastric tissue (proxy for rectal tissue) concentrations by dose

*1.5g dose: 500mg on day 1; gastric acid lowering (pH increasing) drug taken with azithromycin; ** no data

*17 hours post dose; **prostate samples for 12 hrs was at 11-18hrs and for 6-7 days was at 104-122hr; ^gynaecological tissue data for 6-7days was sampled at 4 days and tonsils data for 24hrs was sampled at 9-18hrs; +saliva and gingiva was a 12 hour post dose following a dose of 500mg daily for 3 days; urological tissue includes testicle, epididymis, vas deferens, seminal vesicle/fluid

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Conclusion

- Optimized short courses improves patient compliance and possibly efficacy.
- Short courses, with high 'front end' loading doses ('hit hard, hit early') represents a feasible dosing regimen when doses >1g are required.
- Regimens of 2g over 3 days (1g, 500mg, 500mg) may be feasible for overcoming treatment failure of Mycoplasma genitalium, gonorrhoea and potentially rectal chlamydia infections.